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14. ABSTRACT

Prostate cancer is the second leading cause of cancer death among men in North America, mostly due to a high incidence of cancer cell spreading to bones (metastasis), which is incurable by any currently used regimens. Our long-range goal is to develop an innovative non-invasive approach to reach those metastatic prostate cancer cells via tumor interacting stroma cells and eliminate them on-site through cytotoxic gene delivery. This will be achieved by using engineered mesenchymal stem cells (MSC) as a gene delivery vehicle to reach tumor cells as they tend to serve as stroma bed for tumor growth. We have constructed therapeutic gene delivery vectors (plasmid DNA) and engineered human MSC with the some of the vectors. We also inoculated those engineered MSC together with human prostate cancer cells into immune incompetent mice to examine their interaction and supportive role for the growth of prostate cancer before the initiation of therapeutic treatment. Unfortunately, these on-going experiments were interrupted at this stage by the landfall of Hurricane Katrina. Furthermore, with closure of our research facility and loss of lab personnel on this project, this project is considerably behind our proposed schedule. As LSUHSC reopens and the approval on extension of this project, we believe that we will be able to catch up with our proposed study and draw significant insights during the next 10 -12 months.

15. Subject Terms (keywords previously assigned to proposal abstract or terms which apply to this award)

Mesenchymal stem cells, prostate cancer, targeted gene delivery, gene therapy

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Introduction

Prostate cancer metastases, especially bone metastases, are the major reason account for high mortality of advanced prostate cancer as they can not be reached by any currently used regimens without detrimental side effects to the patients. Even though the exact mechanism of preferential prostate cancer bone metastasis has not yet been well understood, it is speculated that the migration and establishment of these cancer cells in the bone compartment is contributed by the stimulatory and supportive roles of bone marrow stroma cells or mesenchymal stem cells (MSC). We thus hypothesize that targeting the tumor supportive stroma cells via MSC would represent one promising avenue for our long-term goal of developing an innovative non-invasive approach for treating metastatic prostate cancers.

Body

This research project has not been modified from the previously approved proposal and thus the results are presented in accordance with the proposed tasks. Overall, we had initiated most of the planned experiments for task 1 and some of task 2. We also fine tuned some of the experimental conditions for tumor established and bone metastasis. However, due to the landfall of Hurricane Katrina, we lost all the tumor and MSC carrying mice in on-going experiments. Thus, no histological images were obtained from those tumor growing mice.

Task 1. To examine the migration and distribution of GFP gene marked human mesenchymal stem cells within subcutaneous and metastatic LuCap 23.1 tumor in SCID mice and their supportive role in forming tumor-stroma mass and neovasculature.

a. Determine the distribution of GFP transduced human mesenchymal stem cells (MSC) in co-injected subcutaneous LuCaP23.1 tumor nodule and characterization of GFP^+ cell population.

We first implanted tumor, MSC alone or combination of MSC with tumor subcutaneously in immune incompetent SCID and nude mice and observed tumor establishment and growth for two months. In all groups, the growth of tumors was too slow to establish robust, sizable and reproducible tumor mass for histological analyses. We then treated the tumor bearing mice with testosterone (DHT) twice shortly after tumor inoculation, which appeared to moderately enhance tumor growth. Additionally, we also added matrigel to tumor and MSC mix and observed enhanced/accelerated tumor growth within the first 3 weeks post-tumor inoculation. With this modification, we had on-going experiments to examining the interaction and supportive roles of MSC and/or matrigel on tumor growth in nude mice before Katrina arrived. No representative histological comparison was generated.

b. Determine the migration and distribution of GFP marked MSC in LuCaP 23.1 bone metastases and characterization of GFP^+ cell populations.

We inoculated prostate cancer alone or in combination with MSC to tibia bone cavity and examined their establishment in SCID mice. At the early time points, i.e. 20 - 35 days post-tumor inoculation, no obvious tumor mass was identified in the bone sections when prostate cancer was inoculated alone. In contrast, when prostate cancer cells were inoculated together with MSC,

tumor establishment in the bone cavity was observed. Longer-term observation of tumor bearing mice in terms of further metastases was ruined by Hurricane Katrina. In this bone metastasis model, not matrigel is required for tumor establishment.

c. Examine the migration and involvement in neovasculature of intravenously injected GFP-MSC in pre-established bone metastatic LuCaP 23.1.

Not yet started.

Task 2. To examine the therapeutic efficiency in selective elimination of subcutaneous and bone metastatic LuCaP 23.1 upon pro-drug administration and bystander-effect mediated destruction of tumor-stroma mass with modified MSC carrying suicide HSV-TK gene.

a. Construct lentiviral vector carrying HSV-TK (suicide) gene under the control of a hypoxia inducible promoter OBHRE.

Construction of lentiviral vector containing the HSV-TK gene was initiated and some recombinant vectors were obtained, which are yet to be confirmed with restriction enzyme digestions and function assays.

b. Examine the effects of OBHRE-HSV-TK transduced MSC in GCV mediated killing of subcutaneous LuCaP 23.1 tumors.

Not yet started.

c. Determine specific CaP killing through TK gene modified MSC in LuCap32.1 metastasized to bone compartment.

Not yet started.

Key Research Accomplishments

- Growth of human prostate cancer in the presence or absence of human MSC was evaluated in immune incompetent SCID and nude mice;
- We concluded from preliminary studies that subcutaneous growth of prostate cancer requires the support of both MSC and matrigel, whereas intratibia growth of prostate cancer only requires the support of MSC.
- Conditions in experimental protocols for optimal support of establishment and growth of human tumors in immune incompetent mice were determined;
- Lentiviral vector carrying suicide gene HSV-TK was constructed.

Reportable outcome

N/A.

Conclusions

As outlined above, we have made major progresses towards tumor establishment, especially the supportive roles of MSC on subcutaneous and intratibia tumor growth. We also constructed therapeutic vector carrying HSV-TK gene for later use. However, the closure of our research facility and the loss of lab personnel on this project as the results of Katrina, we are considerably behind our proposed schedule. With the recent reopening of LSUHSC, the approval to extend this project, and more importantly recent recruitment of a new post-doctoral fellow, we believe that we will be able to catch up with the proposed study and bring significant insights in the next 10 -12 months.

References

N/A.

Appendices

N/A.